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#9	Search **#3 NOT #4** Field: **Title/Abstract**	14:26:21	8
#4	Search **#2 AND (culture or media or cystein* or sulfat*) AND (toxin or pertussis or PT)** Field: **Title/Abstract**	14:23:01	46
#3	Search **#2 AND (culture or media or cystein* or sulfat*) AND (toxin or pertussis or PT)**	14:18:19	54
#2	**Related Articles** for **PubMed** (Select **12595447**)	14:17:31	268
#1	Search **12595447**	14:17:28	1

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57N

FILE 'HOME' ENTERED AT 18:08:10 ON 15 NOV 2004

L1 2242 (BARIUM OR BACL## OR SULFATE OR SO4## OR CYSTEINE) AND (BACTER? OR PATHOGEN? OR BORDETELLA OR SHIGELLA OR STAPH?) (P) #####TOXIN

L6 706 L5 AND (BACTER? OR CLOSTRID? OR BORDETELLA OR SHIGELLA OR STAPH ?)

(FILE 'HOME' ENTERED AT 18:08:10 ON 15 NOV 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE' ENTERED AT 18:09:47 ON 15 NOV 2004

L1 2242 S (BARIUM OR BACL## OR SULFATE OR SO4## OR CYSTEINE) AND (BACTE
L2 533 S L1 AND (CYSTEINE OR CYS?) (P) TOXIN
L3 37 S L2 AND (SULFATE OR METABOL?) (S) (CYSTEINE OR TOXIN)
L4 24 DUP REM L3 (13 DUPLICATES REMOVED)
L5 765 S L1 AND (SULFATE OR SO4##) (P) TOXIN
L6 706 S L5 AND (BACTER? OR CLOSTRID? OR BORDETELLA OR SHIGELLA OR S
L7 440 S L1 AND (SULFATE OR SO4##) (S) TOXIN
L8 420 S L7 NOT L2
L9 22 S L8 AND (INHIBIT (S) TOXIN)
L10 27 S L7 AND (INHIBIT (S) TOXIN)
L11 31 S L6 AND (INHIBIT (S) TOXIN)
L12 19 DUP REM L11 (12 DUPLICATES REMOVED)

L4 ANSWER 3 OF 24 MEDLINE on STN DUPLICATE 2
AN 2003084092 MEDLINE
DN PubMed ID: 12595447
TI Reduced glutathione is required for pertussis **toxin** secretion by **Bordetella** pertussis.
AU Stenson Trevor H; Patton Angela K; Weiss Alison A
CS Department of Molecular Genetics, Biochemistry, and Microbiology, University of Cincinnati, Cincinnati, Ohio 45267-0524, USA.
NC R01 AI23695 (NIAID)
SO Infection and immunity, (2003 Mar) 71 (3) 1316-20.
Journal code: 0246127. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 20030222
Last Updated on STN: 20030321
Entered Medline: 20030320
AB The abilities of **cysteine**-containing compounds to support growth of **Bordetella** pertussis and influence pertussis **toxin** transcription, assembly, and secretion were examined. **Cysteine** is an essential amino acid for B. pertussis and must be present for protein synthesis and **bacterial** growth. However, **cysteine** can be **metabolized** to **sulfate**, and high concentrations of **sulfate** can selectively inhibit transcription of the virulence factors, including pertussis **toxin** , via the BvgAS two-component regulatory system in a process called modulation. In addition, pertussis **toxin** possesses several disulfide bonds, and the **cysteine**-containing compound glutathione can influence oxidation-reduction reactions and perhaps disulfide bond formation. **Bacterial** growth was not observed in the absence of a source of **cysteine**. Oxidized glutathione, as a sole source of **cysteine**, also did not support **bacterial** growth. **Cysteine**, **cystine**, and reduced glutathione did support **bacterial** growth, and none of these compounds caused modulation at the concentrations tested. Similar amounts of periplasmic pertussis **toxin** were detected regardless of the source of **cysteine**; however, in the absence of reduced glutathione, pertussis **toxin** was not efficiently secreted. Addition of the reducing agent dithiothreitol was unable to compensate for the lack of reduced glutathione and did not promote secretion of pertussis **toxin**. These results suggest that reduced glutathione does not affect the accumulation of assembled active pertussis **toxin** in the periplasm but plays a role in efficient pertussis **toxin** secretion by the **bacterium**.

L4 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:747833 CAPLUS
DN 135:302952
TI Improved method for the production of bacterial toxins
IN Blake, Milan S.; Bogdan, John A., Jr.; Nazario-Larrieu, Javier
PA Baxter International Inc., USA; Baxter Healthcare S.A.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 2001074862 A2 20011011 WO 2001-US10938 20010404
WO 2001074862 A3 20021003
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
US 2002061555 A1 20020523 US 2001-825770 20010404
US 6686180 B2 20040203
US 2002165344 A1 20021107 US 2001-825769 20010404
EP 1268531 A2 20030102 EP 2001-926612 20010404
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2003531586 T2 20031028 JP 2001-572551 20010404
PRAI US 2000-194478P P 20000404
US 2000-194482P P 20000404
WO 2001-US10938 W 20010404
AB Methods and compns. are provided for the enhanced production of **bacterial** toxins in large-scale cultures. Specifically, methods and compns. for reducing **bacterial toxin** expression inhibitors are provided including, but not limited to, addition of **toxin** expression inhibitor binding compds., culture media having reduced concns. of **toxin** inhibitor **metabolic** precursors and genetically modified toxigenic **bacteria** lacking enzymes required to **metabolize** the **toxin** inhibitor **metabolic** precursors.

L4 ANSWER 5 OF 24 MEDLINE on STN DUPLICATE 3
AN 2001551434 MEDLINE
DN PubMed ID: 11598055
TI **Bordetella** pertussis autoregulates pertussis **toxin** production through the **metabolism** of **cysteine**.
AU Bogdan J A; Nazario-Larrieu J; Sarwar J; Alexander P; Blake M S
CS Baxter Healthcare Corporation, Columbia, Maryland 21046-2358, USA.. John_Bogdan@Baxter.com
SO Infection and immunity, (2001 Nov) 69 (11) 6823-30.
Journal code: 0246127. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20011015
Last Updated on STN: 20021218
Entered Medline: 20011205
AB Pertussis **toxin** (Ptx) expression and secretion in **Bordetella** pertussis are regulated by a two-component signal transduction system encoded by the bvg regulatory locus. However, it is not known whether the metabolic pathways and growth state of the **bacterium** influence synthesis and secretion of Ptx and other virulence factors. We have observed a reduction in the concentration of Ptx per optical density unit midway in fermentation. Studies were conducted to identify possible factors causing this reduction and to develop culture conditions that optimize Ptx expression. Medium reconstitution experiments demonstrated that spent medium and a fraction of this medium containing components with a molecular weight of <3,000 inhibited the production of Ptx. A complete flux analysis of the

intermediate **metabolism** of B. pertussis revealed that the sulfur-containing amino acids methionine and **cysteine** and the organic acid pyruvate accumulated in the media. In fermentation, a large amount of internal **sulfate** (**SO4**(2-)) was observed in early stage growth, followed by a rapid decrease as the cells entered into logarithmic growth. This loss was later followed by the accumulation of large quantities of **SO4**(2-) into the media in late-stage fermentation. Release of **SO4**(2-) into the media by the cells signaled the decoupling of cell growth and Ptx production. Under conditions that limited **cysteine**, a fivefold increase in Ptx production was observed. Addition of **barium** chloride (**BaCl2**) to the culture further increased Ptx yield. Our results suggest that B. pertussis is capable of autoregulating the activity of the bvg regulon through its **metabolism** of **cysteine**. Reduction of the amount of **cysteine** in the media results in prolonged vir expression due to the absence of the negative inhibitor **SO4**(2-). Therefore, the combined presence and **metabolism** of **cysteine** may be an important mechanism in the **pathogenesis** of B. pertussis.

L4 ANSWER 8 OF 24 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:176480 BIOSIS
DN PREV200200176480
TI Identification and characterization of a **cysteine** desulfinase gene in Bordetella pertussis.
AU Yuan, W. [Reprint author]; Bogdan, J. A. [Reprint author]; Blake, M. S. [Reprint author]
CS Baxter Healthcare Corporation, Columbia, MD, USA
SO Abstracts of the General Meeting of the American Society for Microbiology, (2001) Vol. 101, pp. 87. print.
Meeting Info.: 101st General Meeting of the American Society for Microbiology. Orlando, FL, USA. May 20-24, 2001. American Society for Microbiology.
ISSN: 1060-2011.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 6 Mar 2002
Last Updated on STN: 6 Mar 2002
AB Many studies have shown that **sulfate** ions inhibit the production of pertussis **toxin** (Ptx). We have shown that sulfur containing amino acids, methionine and **cysteine**, accumulate during fermentation in the late exponential phase of **bacterial** growth in concert with the appearance of **sulfate** anion in the media. Ptx expression begins to wane approximately at the same time as measurable **sulfate** anion can be detected. Our hypothesis is that the accumulation of **sulfate** anion acts as a natural negative feedback inhibitor of Ptx expression. An NIFS-like protein of E. coli has been cloned and reported to have **cysteine** desulfinase activity, removing the **sulfate** ion from **cysteine**. We have identified a similar **cysteine** desulfinase (dsf) gene on a 1.2 Kb DNA fragment from a B. pertussis genomic library. The DNA sequence of the region showed an ORF having a striking sequence homology at the translated protein level with the dsf gene of E. coli. Analysis by Southern blotting, using the full-length gene as the probe, demonstrated that only a single copy was present in the genome of three different B. pertussis strains. To determine the expression pattern of the desulfinase gene in our B. pertussis strain, we performed RT-PCR on total RNA extracted from the cell pellets harvested at different time points during fermentation.

These studies showed that 'cdsf' transcription increased at 10 hours during fermentation, which correlated well with the observed increase of **sulfate** in the media.

L4 ANSWER 9 OF 24 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:176481 BIOSIS
DN PREV200200176481
TI **Bordetella** pertussis auto-regulates pertussis **toxin** production through the **metabolic** conversion of L-**cysteine** to pyruvic acid and **sulfate**.
AU Bogdan, J. A. [Reprint author]; Yuan, W. [Reprint author]; Sarwar, J. [Reprint author]; Alexander, P. [Reprint author]; Blake, M. S. [Reprint author]
CS Baxter Healthcare Corporation, Columbia, MD, USA
SO Abstracts of the General Meeting of the American Society for Microbiology, (2001) Vol. 101, pp. 87. print.
Meeting Info.: 101st General Meeting of the American Society for Microbiology. Orlando, FL, USA. May 20-24, 2001. American Society for Microbiology.
ISSN: 1060-2011.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 6 Mar 2002
Last Updated on STN: 6 Mar 2002
AB Pertussis **toxin** (Ptx) synthesis and secretion in **Bordetella** pertussis is regulated via a two component signal transduction system encoded by the bvg regulatory locus. BvgS, is a sensory protein in the outer membrane that regulates the expression and secretion of Ptx in response to environmental stimuli such as MgSO4, nicotinic acid and growth at low temperatures. Mutations in BvgS, the RNA polymerase alpha subunit and the proteins of the secretory apparatus directly influence Ptx synthesis and secretion. However, it is not known whether the metabolic pathways and growth-state of the **bacteria** influences synthesis and secretion of Ptx and other virulence factors. Previously, we have shown that **sulfate** (**SO4**) appears in the media in B. pertussis fermentation and in turn acts as a negative feedback inhibitor of Ptx expression. **Cysteine** desulfurase is a **metabolic** enzyme that converts L-**cysteine** into pyruvic acid and **SO4**. To determine whether this **metabolic** pathway was involved in Ptx production, experiments were designed that limited the amount of L-**cysteine** in the media. Under these conditions, we observed a delay in the release of internal **SO4** into media and an increase in the amount of Ptx. Cellular extracts were analyzed for the appearance of the Vra-b protein, a marker for the Bvg-phase. In fermentations using limiting amounts of L-**cysteine**, the Vra-b protein was absent. In fermentation runs using standard media, the Vra-b protein appeared following the appearance of **SO4**. We have cloned and sequenced the B. pertussis homologue to the E. coli **cysteine** desulfurase gene. Preliminary results suggest that that there is an increase in **cysteine** desulfurase transcription before the appearance of **SO4** in the media.

L4 ANSWER 10 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2000347465 EMBASE
TI **Toxins**, butyric acid, and other short-chain fatty acids are coordinately expressed and down-regulated by **cysteine** in Clostridium difficile.
AU Karlsson S.; Lindberg A.; Norin E.; Burman L.G.; Akerlund T.

CS T. Akerlund, Department of Bacteriology, Swedish Inst. Infect. Dis. Contr., S-171 82 Solna, Sweden. Thomas.Akerlund@smi.ki.se
SO Infection and Immunity, (2000) 68/10 (5881-5888).
Refs: 27
ISSN: 0019-9567 CODEN: INFIBR
CY United States
DT Journal; Article
FS 004 Microbiology
LA English
SL English
AB It was recently found that a mixture of nine amino acids down-regulate Clostridium difficile **toxin** production when added to peptone yeast extract (PY) cultures of strain VPI 10463 (S. Karlsson, L. G. Burman, and T. Akkerlund, Microbiology 145:1683-1693, 1999). In the present study, seven of these amino acids were found to exhibit a moderate suppression of **toxin** production, whereas proline and particularly **cysteine** had the greatest impact, on both reference strains (n = 6) and clinical isolates (n = 28) of C. difficile (>99% suppression by **cysteine** in the highest **toxin**-producing strain). Also, **cysteine** derivatives such as acetylcysteine, glutathione, and **cystine** effectively down-regulated **toxin** expression. An impact of both **cysteine** and **cystine** but not of thioglycolate on **toxin** yield indicated that **toxin** expression was not regulated by the oxidation-reduction potential. Several **metabolic** pathways, including butyric acid and butanol production, were coinduced with the **toxins** in PY and down-regulated by **cysteine**. The enzyme 3-hydroxybutyryl coenzyme A dehydrogenase, a key enzyme in solventogenesis in Clostridium acetobutylicum, was among the most up-regulated proteins during high **toxin** production. The addition of butyric acid to various growth media induced **toxin** production, whereas the addition of butanol had the opposite effect. The results indicate a coupling between specific **metabolic** processes and **toxin** expression in C. difficile and that certain amino acids can alter these pathways coordinately. We speculate that down-regulation of **toxin** production by the administration of such amino acids to the colon may become a novel approach to prophylaxis and therapy for C. difficile-associated diarrhea.

L4 ANSWER 14 OF 24 EMBASE
on STN
AN 94344976 EMBASE
DN 1994344976
TI Toxin production by Clostridium difficile in a defined medium with limited amino acids.
AU Yamakawa K.; Kamiya S.; Meng X.Q.; Karasawa T.; Nakamura S.
CS Department of Bacteriology, School of Medicine, Kanazawa University, 13-1 Takara-machi,Kanazawa, Ishikawa 920, Japan
SO Journal of Medical Microbiology, (1994) 41/5 (319-323).
ISSN: 0022-2615 CODEN: JMMIAV
CY United Kingdom
DT Journal; Article
FS 004 Microbiology
LA English
SL English
AB Basal defined medium (BDM) containing vitamins, minerals and seven amino acids - (/L) tryptophan 0.1 g, methionine 0.2 g, valine 0.3 g, isoleucine 0.3 g, proline 0.3 g, leucine 0.4 g and **cysteine** 0.5 g - which appeared to be essential for good growth of Clostridium difficile was prepared. Addition of glycine 0.2 g/L and threonine 0.4 g/L to BDM

produced better growth of strain VPI 10463, and this defined medium was designated minimum amino acid-defined medium (MADM). Production of **toxins** A and B by strain VPI 10463 in 6 x MADM containing (/L) tryptophan 0.6 g, methionine 1.2 g, valine 1.8 g, isoleucine 1.8 g, proline 1.8 g, leucine 2.4 g, **cysteine** 0.5 g, glycine 0.2 g and threonine 0.4 g, was much greater than in MADM. **Toxin** production by 20 C. difficile strains was examined in two defined media - 6 x MADM and complete amino acid-defined medium (CADM) containing 18 amino acids - and one complex medium, modified brain heart infusion medium (m-BHI). Simultaneous production of **toxins** A and B by all test strains was demonstrated in m-BHI and the two defined media. It was also shown that 6 x MADM was generally better than CADM and as effective as m-BHI for stimulating **toxin** production by 13 strains. This defined medium would be useful for studies on the physiology, **metabolism** and **pathogenicity** of C. difficile.

NSWER 18 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1987:421983 CAPLUS
DN 107:21983
TI Large-scale cultivation of **Bordetella** pertussis for production of pertussis **toxin**
IN Sekura, R. D.
PA United States Dept. of Health and Human Services, USA
SO U. S. Pat. Appl., 17 pp. Avail. NTIS Order No. PAT-APPL-6-889 621.
CODEN: XAXXAV
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 889621	A0	19861205	US 1986-889621	19860728
	US 5338670	A	19940816	US 1992-989908	19921211
PRAI	US 1986-889621		19860728		
	US 1989-338459		19890417		
	US 1990-504022		19900404		

AB B. pertussis Is cultivated and production of its **toxin** enhanced by (1) incorporation of an antifoam agent; (2) controlling aeration by using pure O or O-enriched air; and (3) regulation of Fe content in the medium. Thus, the microorganism was precultured in a medium containing 10 mg FeSO4/L and then cultured in a medium (pH 7.4) containing Na glutamate 965, proline 21.6 g, anti-foam C 45 mL and salts (supplemented with **cystine** 4.0, ascorbic acid 2.0, niacin 0.4, and reduced glutathione 10 g) at 36° with agitation. O concentration was maintained at 40% of saturation **Bacterial** growth and pertussis **toxin** production reached a maximum in .apprx.20 h. The maximum **toxin** value was approx. 6 mg/L.

L4 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1961:119606 CAPLUS
DN 55:119606
OREF 55:22546d-h
TI Detoxification function of depot iron. II. Animal experimental studies on the detoxification of tetanus toxin by hemosiderin and reducing substances
AU Heilmeyer, L.; Wohler, F.
CS Med. Univ.-Klinik, Freiburg i. B., Germany
SO Klinische Wochenschrift (1961), 39, 563-81
CODEN: KLWOAZ; ISSN: 0023-2173
DT Journal
LA Unavailable
AB cf. CA 55, 8591e. Incubation of a mouse lethal dose of tetanus **toxin** with 2 mg. hemosiderin for 6 hrs. at pH 5.5 and 37°

completely protected the animals against the **toxin**. The **toxin** was also inactivated when it was incubated with hemosiderin plus ascorbic acid or **cysteine** or with FeSO4 or FeCl3. Incubation with distilled water did not appreciably affect activity of the **toxin** and incubation with ferritin only slightly prolonged survival time. In Fe-depleted mice the survival time after injection of **toxin** was significantly diminished. Brief incubation (10-60 min.) of **toxin** with ascorbic acid, FeSO4, or Reducdyn (preparation of DL-homocysteine thiolactone, L-**cysteine**, and fructose) produced inactivation but shorter times were not effective. Similar results were obtained in rats and rabbits. FeSO4, and to a lesser extent the other 2 compds., increased the survival time of mice when it was injected intraperitoneally as the **toxin** was injected subcutaneously. When these compds. were injected 30 min. later than the **toxin**, they afforded no protection. Oral doses of FeSO4 also partially protected against subsequently injected **toxin**. These and earlier results indicate that Fe ions released by reducing substances from Fe deposits, particularly in reticuloendothelial cells in sites of inflammation, may function in the inactivation of **bacterial toxins**.

L12 ANSWER 6 OF 19 MEDLINE on STN DUPLICATE 2
AN 2000233619 MEDLINE
DN PubMed ID: 10770786
TI Antibacterial agents and release of periplasmic pertussis **toxin** from **Bordetella** pertussis.
AU Craig-Mylius K A; Weiss A A
CS Department of Molecular Genetics, Biochemistry, and Microbiology, University of Cincinnati, Cincinnati, Ohio 45267-0524, USA.
NC RO1 AI23695 (NIAID)
SO Antimicrobial agents and chemotherapy, (2000 May) 44 (5) 1383-6. Journal code: 0315061. ISSN: 0066-4804.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 20000525
Last Updated on STN: 20021218
Entered Medline: 20000518
AB Pertussis **toxin** accumulates in the periplasm of **Bordetella** pertussis prior to secretion, and we examined its fate following treatment with antimicrobial agents. Both antibiotics that **inhibit** protein synthesis (erythromycin and chloramphenicol), transcription (rifampin), or cell wall biosynthesis (cefoperazone and piperacillin) and magnesium **sulfate** (which **inhibits** transcription of pertussis **toxin**, but not **bacterial** growth) did not prevent release of preformed **toxin**. In contrast, agents that affect **bacterial** membranes, such as polymyxin B, lidocaine, procaine, and ethanol, inhibited release of preformed pertussis **toxin**. These results suggest new protein synthesis is not required for pertussis **toxin** secretion, but a functional membrane complex is required.